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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,480	08/13/2002	Robert Heger	49619	4809

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EXAMINER	
BENNETT, RACHEL M	

ART UNIT	PAPER NUMBER
1615	16

DATE MAILED: 10/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/857,480	Applicant(s) HEGER ET AL.	
	Examiner Rachel M. Bennett	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cov r sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The examiner acknowledges receipt of Amendment B filed 8/15/03.

Specification

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 15-18, 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stainmesse (US 5133908).

Applicants claim a process for preparing a nano-particulate preparation of a pharmaceutical or cosmetic active ingredient with a core/shell structure, in which the X-ray amorphous active ingredient is present in the core together with one or more polymers and the shell consists of a stabilizing coating matrix, comprising mixing the active ingredient/polymer

solution or precipitate with the aqueous solution of the polymeric coating material continuously in a mixing chamber by spraying the two components as a compact jet into a mixing chamber.

Stainmesse et al disclose a process for the preparation of dispersible colloidal systems of a substance in the form of spherical particles of the matrix type and of a size less than 500 nm (nanoparticles), comprising: (1) the preparation of a liquid phase consisting essentially of a solution of the substance in a solvent or in a mixture of solvents to which may be added one or more surfactants, (2) the preparation of a second liquid phase consisting essentially of a non-solvent of a mixture of non-solvents for the substance and to which may be added one or more surfactants, the non-solvent or the mixture of non-solvents for the substance being miscible in all proportions with the solvent or the mixture of solvents for the substance, (3) the addition of one of the liquid phases prepared in (1) or (2) to the other with moderate stirring so as to produce a colloidal suspension of nanoparticles of the substance and, (4) if desired, the removal of all or part of the solvent or the mixture of solvents for the substance and of the non-solvent or the mixture of non-solvents for the substance so as to produce a colloidal suspension of nanoparticles of the desired concentration or to produce a powder of nanoparticles. Said substance may be a protein. The nanoparticle may be used in chemistry, biochemistry, pharmacy, medicine, and cosmetics. In example 5, 5mg indomethacin and 125 mg D,L-polylactic acid are dissolved in 25 ml acetone. In order to produce the aqueous phase, 125 mg Poloxamer 188 are dissolved in 50 ml water. The acetone phase is stirred into the aqueous phase. Nanoparticles are obtained with an average diameter of 180 nm. After the acetone is evaporated under a reduced pressure, the remaining aqueous suspension can be further concentrated. Active substance resorption characteristics were examined using a series of tests on rats, to which and nanoparticle

suspension was administered orally or intravenously. The production method described in Stainmesse corresponds to the method defined in the instant application, in which D,L-polylactic acid represents the core polymer and Poloxamer 188 the sheathing polymer (see instant specification, page 5, lines 33-37, and page 4, lines 21-23). It could therefore also be assumed that the nanoparticles obtained in the instant application (see page 1, lines 7-11, of the instant application) have a core-shell structure in which the amorphous precipitated active substance is present in the core (compare with Example 14 of Stainmesse) in a matrix of D,L-polylactic acid, while the Poloxamer forms an external stabilizing layer. The aqueous nanoparticles suspension corresponds to the hydrosol of the instant claims. Stainmesse discloses not disclose mixing the active ingredient/polymer solution or precipitate with the aqueous solution of the polymeric coating material continuously in a mixing chamber.

Absent unexpected results, it is the position of the examiner it would have been obvious to one of ordinary skill in the art to have mixed the composition either in a batch, as suggested by the Stainmesse, or continuously, as both are well known in the art. Both processes result in a precipitation, wherein the suspension or colloid is converted into a dry powder. Stainmeese teaches the nanoparticles obtained have an average diameter of 180 nm, therefore, meeting the limitations of the instant claims. Applicants themselves disclose the mixing process can be carried out batchwise or continuously (see page 9, lines 4-5) in order to obtain the desired particle size. Therefore, there is no criticality in mixing continuously.

4. Claims 15-18, 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over List et al. (US 5389382).

Applicants claim a process for preparing a nano-particulate preparation of a pharmaceutical or cosmetic active ingredient with a core/shell structure, in which the X-ray amorphous active ingredient is present in the core together with one or more polymers and the shell consists of a stabilizing coating matrix, comprising mixing the active ingredient/polymer solution or precipitate with the aqueous solution of the polymeric coating material continuously in a mixing chamber by spraying the two components as a compact jet into a mixing chamber.

List discloses a hydrosol of a pharmacological active agent in an intravenous applicable, stabilized, pharmaceutically acceptable form, which form is suspended or is dry and re-suspendable in an aqueous medium. The hydrosol contains solid active agent particles. See abstract. The hydrosol is started from a solution of a hardly water-soluble active substance in a water-miscible solvent. This solution is mixed with a relatively large amount of water containing a water-soluble colloid, for example gelatin. Alternatively or additionally, a water-insoluble colloid can be dissolved in the organic solvent. The colloid stabilized the active substance hydrosol formed when the phases are brought together. The organic solvent is then removed. In Examples 4, 9 and 10, the pharmacologically active substance and ethyl cellulose re first dissolved in ethanol. The ethanolic phase is then stirred into an aqueous phase containing gelatin or a collagen hydrolysate. The ethanol is evaporated. The average particle diameter of the suspended particles is of 245 nm, 129nm, and 320 nm. The nanoparticles and their hydrosols correspond to the preparations defined in instant claims. Ethyl cellulose acts in this case as core polymer, the sheathing polymer is gelatin or collagen hydrolysate. List discloses not disclose mixing the active ingredient/polymer solution or precipitate with the aqueous solution of the polymeric coating material continuously in a mixing chamber.

Absent unexpected results, it is the position of the examiner it would have been obvious to one of ordinary skill in the art to have mixed the composition either in a batch, as suggested by the List, or continuously, as both are well known in the art. Both processes result in a precipitation, wherein the suspension or colloid is converted into a dry powder. List teaches the size of the suspended particles is 245 nm, 129nm, and 320 nm, therefore, meeting the limitations of the instant claims. Applicants themselves disclose the mixing process can be carried out batchwise or continuously (see page 9, lines 4-5) in order to obtain the desired particle size. Therefore, there is no criticality in mixing continuously.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 15-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over List et al. (US 5389382) in view of Liverside et al. (US 5145684).

Applicants claim a process for preparing a nano-particulate preparation of a pharmaceutical or cosmetic active ingredient with a core/shell structure, in which the X-ray amorphous active ingredient is present in the core together with one or more polymers and the shell consists of a stabilizing coating matrix, comprising mixing the active ingredient/polymer solution or precipitate with the aqueous solution of the polymeric coating material continuously in a mixing chamber by spraying the two components as a compact jet into a mixing chamber.

List discloses a hydrosol of a pharmacological active agent in an intravenous applicable, stabilized, pharmaceutically acceptable form, which form is suspended or is dry and re-suspendable in an aqueous medium. The hydrosol contains solid active agent particles. See abstract. The hydrosol is started from a solution of a hardly water-soluble active substance in a water-miscible solvent. This solution is mixed with a relatively large amount of water containing a water-soluble colloid, for example gelatin. Alternatively or additionally, a water-insoluble colloid can be dissolved in the organic solvent. The colloid stabilized the active substance hydrosol formed when the phases are brought together. The organic solvent is then removed. In Examples 4, 9 and 10, the pharmacologically active substance and ethyl cellulose re first dissolved in ethanol. The ethanolic phase is then stirred into an aqueous phase containing gelatin or a collagen hydrolysate. The ethanol is evaporated. The average particle diameter of the suspended particles is of 245 nm, 129nm, and 320 nm. The nanoparticles and their hydrosols correspond to the preparations defined in instant claims 1 and 9. Ethyl cellulose acts in this case as core polymer, the sheathing polymer is gelatin or collagen hydrolysate. List discloses a hydrosol of a pharmacological active agent in an intravenous applicable, stabilized, pharmaceutically acceptable form, which form is suspended or is dry and re-suspendable in an aqueous medium. List does not specifically disclose casein or sodium caseinate as a coating matrix.

Liversidge et al. discloses surface modified drug nanoparticles. Dispersible particles consisting essentially of a crystal-line drug substance having a surface modifer absorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less thatn about 400nm. Pharmaceutical compositions containing the particles exhibit unexpected

bioavailablity and are useful in methods of treating mammals. See abstract. Suitable surface modifiers can preferably be selected from known excipients. Representative examples include gelatin, casein, lecithin, gum acacia, methylcellulose, etc. See col. 4 lines 34-64.

Absent unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of List by substituting casin as taught by Liversidge for gelatin as the coating polymer because of the expectation of exhibit unexpected bioavailablity and are useful in methods of treating mammals as taught by Liverside. Both gelatin and casein are known excipients used as surface modifiers. Therefore, substituting one for another would not require undue experimentation and one of ordinary skill in the art would expect similar results.

Response to Arguments

7. Applicant's arguments, filed 8/15/03, with respect to 35 USC 102(b) have been fully considered and are persuasive. The rejections under 102(b) have been withdrawn.

8. Applicant's arguments filed 8/15/03 with regards to 35 USC 103(a) have been fully considered but they are not persuasive.

Applicants argue the particles disclosed by Liverside contain crystalline drug substance and are obtained by a process of wet grinding of a liquid dispersion of the drug substance. The examiner refers to Liverside, wherein casin is taught as the coating polymer because of the expectation of exhibit unexpected bioavailablity and are useful in methods of treating mammals. Liverside is used to teach an alternative coating polymer. Therefore, absent unexpected results, it is the position of the examiner the polymer coating taught by Liverside may be used with both

amorphous and crystalline drugs with the expectation of exhibiting unexpected bioavailablity and are useful in methods of treating mammals as taught by Liverside. Both gelatin and casein are known excipients used as surface modifiers. Therefore, substituting one for another would not require undue experimentation and one of ordinary skill in the art would expect similar results. Therefore, the rejection is maintained.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

R. Bennett
October 29, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600